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REVIEW OF NUTRITION RESEARCH

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VOLUME 22 · NO. 4
OCT. - DEC. 1961

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BORDEN'S REVIEW OF NUTRITION RESEARCH

Reviews and summaries of research information concerning nutrition and foods. Published quarterly, by THE BORDEN COMPANY; officers of the Company: Harold W. Comfort, president; E. L. Noetzel, vice president and treasurer; D. T. Orton, secretary. Editorial office: 350 Madison Avenue, New York 17, N. Y.

The Magnesium Deficiency Tetany Syndrome in Man

Warren E. C. Wacker, M.D.* and Bert L. Vallee, M.D.†

Magnesium is an essential nutrient for animals and plants, suggesting that a dietary inadequacy of this ion might readily result in deficiency disease. Indeed, such deficiency states have been induced in animals. Tetany and convulsions, subsequent to experimental magnesium deficiency, were first shown to occur in rats, in 1932,[90] and later in many other animal species.[129, 138, 14] Spontaneous magnesium deficiency tetany has been observed and well characterized in cattle.[44, 20, 22, 146]

Experimental efforts to induce a simple dietary magnesium deficiency in healthy men have proved unsuccessful.[53] Although decreases in the concentration of serum magnesium accompany a considerable number of pathologic states in humans, it is uncertain that this is a reflection either of a negative magnesium balance or of a causal relation to the underlying process. Certainly, attempts to implicate magnesium deficiency as the etiologic factor in any of these conditions have not withstood critical examination. The varieties of neuromuscular aberrations credited to magnesium deficiency are so numerous that they do not add specificity to knowledge of the metabolic functions of this element.

The recognition of human illness resulting from electrolyte deficiencies has been a direct consequence of the development of simple, accurate and rapid analytical technics for the measurement of these metabolites. The strides made in the recognition of abnormalities in the metabolism of sodium and potassium are a telling documentation of this statement, since they coincide with the development of the flame photometer during the last decade.

The failure to correlate magnesium deficiency in man directly with a specific clinical entity has stemmed almost solely from the inadequacy of the methods employed for the determination of magnesium in biologic materials. This is a problem which has been overcome recently by the development of a flame spectrometer.[165] Almost as a direct consequence of these circumstances, a new specific clinical entity, *human* magnesium deficiency tentany, has been described. This syndrome is virtually identical to that of hypocalcemic tetany, from which it can be differentiated only by chemical means. Its manifestations correspond almost exactly to those seen in magnesium deficient animals. In each of the patients in whom the disease has been observed, the parenteral administration of magnesium sulfate promptly and completely reversed the symptoms, signs and chemical changes of the syndrome. An appreciation of the clinical consequences of magnesium deficiency resulting in tetany requires an understanding of the biochemical and physiological actions of this ion.

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Body Content

An accurate measurement of the human body content of magnesium was not made until quite recently.[169] The adult body contains from 21 to 28 grams of magnesium, or about 43 mg/kg of fat-free tissue. At birth, the concentration is lower but it rises rapidly thereafter.[67] About half of the total body content is in bone, the ash containing 0.5 to 0.7 per cent magnesium.[169] When radioactive magnesium is injected into either dogs or men, it rapidly equilibrates with a volume greater than that of the extracellular space. The total rapidly exchangeable magnesium, calculated from these data, is much smaller than the total body content. This indicates that a large fraction of the total magnesium, presumably in bone, does not rapidly equilibrate with the injected isotope.[60]

Body Distribution

Magnesium is similar to potassium in its distribution within the body. The intracellular concentration exceeds the extracellular by a wide margin. The highest concentrations are in the liver and striated muscle, which contain about 20 m Eq./L.[48, 33, 36, 12, 144] The brain and kidney contain about 17 and 13 m Eq./L, respectively, while the red cell concentration is about 6 m Eq./L.[144]

The magnesium concentration of normal serum is seen to vary somewhat, according to the analytical method employed to measure it. The mean serum content has been variously reported as 1.8 to 2.1 m Eq./L, and the range has been found to be from 1.4 to 2.5 m Eq./L.[165, 147, 167, 151, 73] The serum content of infants and children is virtually the same as that of adults.[24, 145]

A portion of the serum magnesium is bound to protein. In the physiological pH range, about 35 per cent of the total magnesium is protein bound, an amount which is almost identical to that of calcium; this similarity extends over a wide range of hydrogen ion concentrations.[30]

The magnesium content of the cerebrospinal fluid is considerably higher than that of serum, the mean ranging from 2.4 to 3.0 m Eq./L.[151, 72] Gastric juice contains about 1.0 m Eq./L.

Biochemistry

Magnesium has been found to be an activator for many enzymes *in vitro*. In 1927, Erdtmann[51] discovered that magnesium ions added to the reaction mixture increased the activity of mammalian alkaline phosphatase. Since then a host of enzymes have been found to be activated by magnesium. Unfortunately, it is not possible to translate these *in vitro* effects, with absolute certainty, directly to physiologic events in the living animal. Most of the studies have been performed on isolated enzyme systems where magnesium ions were simply added to a given enzyme under observation, and the resulting increase in activity was measured. In most instances, these enzymes are also active in the absence of added magnesium ions and in many cases another metal ion may be substituted. Thus, it has not been possible to prove an absolute requirement for magnesium. On this basis, a definitive physiologic role for magnesium in these systems cannot be

assigned. In but a few instances — oxidative phosphorylation, for example — has the *in vitro* effect of magnesium been shown to have a counterpart *in vivo*.

Despite the lack of conclusive evidence for a physiologic role of magnesium in enzymatic activation, inferential reasoning strongly suggests a significant role of this ion in intracellular catalysis. It is an activator for numerous enzymes. Among them are the enzymes catalyzing reactions involving ATP, which split or transfer phosphate groups. Since ATP is required in such diverse functions as muscle contraction, in protein, fat, nucleic acid and coenzyme synthesis, in glucose utilization, in methyl group transfer, in sulfate, acetate and formate activation, and in oxidative phosphorylation, it may be inferred that the action of magnesium extends to all the major anabolic and catabolic processes. In addition, this ion, together with thiamine pyrophosphate, is a cofactor in decarboxylation. Finally, certain peptidases require the metal for activity. It is not possible to include all the enzymes which are activated by magnesium here; the literature is sufficiently extensive to require independent coverage. Therefore, only the major enzymes of each group will be mentioned along with the pertinent bibliography.

The alkaline phosphatases and pyrophosphatases obtained from various mammalian sources, as well as from lower forms, are activated by magnesium.[1-3, 5, 10, 40, 51, 84, 88, 98, 155, 159] Prostatic acid phosphatase is also activated by magnesium.[128, 139]

All of the enzymes that catalyze the transfer of phosphate from ATP to a phosphate receptor, or from a phosphorylated compound to ADP, are activated by magnesium. In most instances they also are activated by manganese. Recent studies, carried out on highly purified enzymes, indicate that an ATP magnesium complex may be the active enzymatic substrate. This conclusion is suggested since ATP forms a 1:1 complex with magnesium,[125] and, moreover, maximal activation occurs when the ratio of magnesium to ATP in the reaction mixture is one.[130, 94, 103, 78]

Among the enzymes of particular importance are: hexokinase;[104, 32, 95] fructokinase;[35] creatinine transphosphorylase;[25] phosphopyruvic transphorylase;[27] phosphoglyceric transphosphorylase;[28] acetyltransphosphorylase;[86] diphosphopyridine nucleotide phosphorylase;[89] and phosphoglucomutase.[34, 83] The action of magnesium in these systems has been reviewed in detail.[96]

Magnesium is an activator for all of the enzymes that require thiamine pyrophosphate as a cofactor. One of them, yeast carboxylase, has been isolated in relatively pure form and found to contain the metal in stoichiometric amounts.[93, 63] Mammalian carboxylases obtained from heart muscle also require magnesium,[64] as does the pyruvic oxidase systems of brain.[127]

Enolase, which catalyzes the dehydration of D-2-phosphoglyceric acid, has been extensively studied with regard to its magnesium activation.[168, 108, 170, 171]

Leucine amino peptidase requires magnesium as a cofactor.[15-17, 85, 141, 148]

The effect of magnesium on mitochondrial oxidative phosphorylation is of particular interest. It constitutes one of the rare instances where the *in vitro* activating effect seems to have a counterpart *in vivo*. A requirement for mag-

nesium ions was demonstrated in the earliest studies of this system.[99, 134, 135] However, the role of the metal has not been studied thoroughly. The comment has been made that "the requirement for magnesium has been so unquestioningly accepted that no studies have been reported on its mode of action.[1, 96] Mitochondria obtained from magnesium deficient rats are incapable of performing oxidative phosphorylation. This indicates that the role of magnesium in this isolated system may have a similar representation in the living organism.[164] It is substantiated further by the observation that the magnesium content of mitochondria of these animals is significantly lower than normal.[157]

Thyroxin added to mitochondrial preparations *in vitro* produces uncoupling of oxidative phosphorylation.[11, 123] A similar effect has been observed in the mitochondria of thyrotoxic rats.[80] These effects can be overcome either by the addition of magnesium ions to the isolated system or by increasing the intake of magnesium in the case of the thyroxin fed animals.[163]

Intake, Needs and Absorption

Magnesium is relatively abundant in foodstuffs; green plants contain large amounts of it owing to its presence in the porphyrin moiety of chlorophyll. The daily intake of magnesium on an average diet is about 300 mg. A daily ingestion of 250 mg. for an adult is considered adequate; during pregnancy and lactation 400 mg. are required.[158] The need for infants is said to be 150 mg. a day.[43]

The common soluble magnesium salts are readily absorbed from the small intestine. Variation of pH induced by feeding either sodium carbonate or hydrochloric acid does not affect the absorption.[41] There is no known factor which controls the absorption of magnesium in a manner similar to that of vitamin D in calcium absorption.

The stool magnesium represents that portion of the ingested ion which is not absorbed;[156] it varies, therefore, with the magnesium intake. The bowel does not represent a major excretory pathway for magnesium in man.[37, 112, 113, 118, 149]

Urinary Excretion

In normal adults about 60 to 200 mg. a day are excreted in the urine. On a controlled diet containing 260 mg. of magnesium a day, normal females excreted an average of 96.2 mg. in the urine.[100] The mean 24-hour urine content of 12 normal men on an unrestricted diet was 162 ± 43 mg.[165]

Precise knowledge of all the factors regulating the urinary excretion of magnesium is not available. In dogs, administration of parathyroid hormone causes an increase in the urinary output for the first three days but has no apparent effect thereafter.[137] Similar effects, to be discussed later, have been reported in humans with hyperparathyroidism. In rats, the administration of aldosterone to either normal or adrenalectomized animals causes an increase in the urinary magnesium excretion.[71]

Magnesium is filtered by the glomerulus and is reabsorbed by the tubules; however, the amount in the reabsorbed fraction is not known.[77] It may, like potassium, be excreted by the tubules; the aglomerular fish excretes magnesium

by this mechanism[18] Several studies in dogs employing the *stop-flow* technique have demonstrated secretion of magnesium by the distal tubules.[59, 124] The ratio of filtered to excreted magnesium may exceed unity during the constant infusion of large amounts of the ion in this species.[49]

Effect on Body Temperature

In lower animals there is a relationship between the body temperature and the serum magnesium concentration. A marked increase in the serum content occurs with hibernation in a number of species.[153, 136, 106] It has been suggested that the depressing action of magnesium on the central nervous system may operate to maintain the hibernating state.[153] Similar increases in the serum content of non-hibernating species may be induced by lowering the body temperature.[132, 9, 133] Moreover the administration of magnesium sulfate to dogs decreases the body temperature regardless of the existing ambient temperature.[76] Variations in serum magnesium concentration with changes in body temperature have not been reported in humans.

Magnesium Deficiency

Magnesium was first shown in 1926 to be essential for normal animal growth. Young mice on a magnesium-deficient diet showed arrested growth after nine to thirteen days; death ensued if the diet was continued for twenty-four to thirty-five days. Controls on the same diet supplemented with magnesium grew normally; deficient animals resumed a normal growth rate when given magnesium even in the late stages of the experiment.[101]

In 1932, Kruse, Orent and McCollum induced magnesium deficiency in rats and described the now classical syndrome that attends this disease.[90] Vasodilatation manifested by erythema and hyperemia appeared within three to five days, followed by pallor and cyanosis twelve days later. Concomitantly, the animals exhibited signs of increasing neuromuscular hyperirritability, culminating in generalized seizures. Chronic deficiency in animals surviving for a long time was manifested by alopecia, trophic skin lesions, hemotomas of the ear lobes, and swollen hyperemic gums. These experiments have been confirmed and extended.[27, 65, 66, 68, 140]

The similarity of magnesium deficiency to hypocalcemic tetany, including the lowered threshold sensitivity, was pointed out early.[92]

Pathologic changes have been demonstrated in the heart, vascular system, kidneys, liver and brain. Since the preparation of the diets also removed other nutrients, the essential role of which was not known at the time of many of the early studies, some uncertainty exists in assigning all of the observed changes solely to magnesium deficiency.

Necrotic lesions, without calcification, in both the glomeruli and tubules of the kidney have been described.[27] Tubular degeneration and fibrosis with casts in the medullary loops and collecting tubules were seen in another study; the cortex showed glomerular degeneration with periglomerular fibrosis.[14, 169]

In one study, the pathologic changes were chiefly confined to the liver; two different types of damage were seen. Grossly, a dark-red area appeared in which the lobulation of the liver stood out in mosaic; there was no particular site of distribution of this lesion: microscopically, there was periportal necrosis and round-cell infiltration along with extensive hepatocellular degeneration. In the other type, the livers were contracted by fibrosis, subsequent to the degeneration of hepatic cells which appeared homogeneous and hyaline-like.[140]

Greenberg and his co-workers[65, 66, 68] have carried out an extensive study of the pathology of magnesium deficiency in rats. The animals were fed a synthetic diet low in magnesium but supplemented with all of the known essential nutrients. Two distinct histological lesions were observed:

> (1) After one or two weeks, inflammatory, necrotic foci appeared about small blood vessels. Later, these became filled with macrophages and eventually became fibrotic. They were widely distributed throughout the body, in the esophagus, trachea, skin and subcutaneous tissue, mesenteric fat, fibrous septa of skeletal muscle, adipose tissue, subepicardial fat, myocardium and subendocardium.
>
> (2) The second lesion consisted of calcium casts in the convoluted and collecting tubules of the kidneys; it appeared only after twenty-five days of the experimental diet but was consistent thereafter. No alterations were found in either the liver or the cerebellum,[92] although a cerebellar lesion consisting of degeneration of the Purkinje cells has been described by others.[14]

The reasons for these differences in experimentally induced pathology can only be conjectured; it is well to point out, however, that the earlier diets [140] lacked essential nutrients, while the later diets were supplemented.[105] Similar experimental differences are reflected in the resulting pathology of other species (*vide infra*).

The serum magnesium concentrations of deficient rats fall from 3 mg. per 100 ml. to about 1 mg. per 100 ml. after seven to nine days of the deficient diet. A similar decrease occurs in the red-cell magnesium content, which falls from 7 mg. per 100 ml. to 2 mg. per 100 ml. after eleven days; the content of other soft tissues does not change. The whole-body content and that of bone fall markedly and there is a concomitant increase of the whole-body calcium content.[161] Deficient animals, fed a diet high in magnesium, rapidly accumulate large quantities of the ion in bone. These facts are interpreted by some to indicate that bone is the magnesium reservoir intended to meet soft-tissue needs during deficiency.[42]

Five milligrams of magnesium per 100 gm. of food prevents the signs of deficiency and promotes normal growth. Several factors, however, increase the magnesium requirement of the rat. Large amounts of calcium aggravate the severity of magnesium deficiency and a greater dietary intake is required to prevent it.[160] A high protein intake also increases the requirement and causes deficiency symptoms to appear on a diet of normal magnesium content.[31] Mag-

nesium-deficient rats also fail to synthesize protein normally.[91, 116, 117] In the rat, feeding a high calcium and normal magnesium diet produces an alkalinization of urine, calcinuria and renal calculi. The serum magnesium concentration of these animals is low while that of calcium is increased.[38] The pathogenesis of this experimental disease is not unlike that which attends the development of the "milk-alkalai" syndrome in man. Finally, the failure of rats to gain weight while receiving thyroxin can be overcome by supplementing the diet with large amounts of magnesium.[163]

The metabolic rate of magnesium-deficient rats is 125 per cent higher than that of control animals kept at the same weight, these controls require only 83 per cent of the total calories required by the deficient animals to maintain their weight.[87] There is no evidence that this is related to a disturbance of thyroid function.

Magnesium Deficiency in Cattle

Two types of magnesium deficiency occur in cattle. The first develops in animals raised exclusively on whole milk. The second is an endemic disease known as *grass tetany,* which, as the name implies, develops on forage diets.

The milk-diet deficiency was the first to be observed but was not then attributed to magnesium deficiency. Two bull calves, reared on a diet consisting exclusively of whole milk, failed to grow, developed skin lesions and neuromuscular hyperirritability and died of convulsions. At autopsy, renal lesions were observed.[114] Twelve years later, this disease was discovered to be due to a lack of dietary magnesium. At that time, 20 calves were reared on a diet consisting of whole milk supplemented with cod-liver oil, manganese, silicon, aluminum, iron and copper. The animals developed tetany and some died of convulsions. The serum calcium and phosphorus concentrations were normal, but the magnesium concentrations were significantly decreased.[44] The endocardium, the aorta and other large arteries of these animals were calcified. Similar lesions were found in the muscles, diaphragm and spleen, and in some of the animals the renal tubules were severely damaged. A periportal fibroblastic reaction in the liver was also noted.[122]

In a similar study, the experimental animals were fed a synthetic diet analogous in composition to whole milk, but supplemented with all of the known vitamins plus iron, manganese, copper, zinc, cobalt, iodine, fluoride, and an alcohol extract of liver. These calves developed the typical signs of magnesium deficiency—irritability, tetany and convulsions—and died. The marked vasodilatation noted in the rat was not observed. Symptoms did not occur until the serum concentration had fallen from a normal of 2.2 to 2.4 mg. per 100 ml. to below 0.7 mg. per 100 ml. The rate of decrease of the serum concentration was exponential and inversely proportional to the total magnesium content of the diet. The normal magnesium requirement was 16.2 mg. per kilogram a day. The serum concentrations of calcium and phosphorus did not change. Thrombosis and perivascular necrosis of small blood vessels in many tissues was the prominent

histological lesion, similar to that described in the rat.[105] The liver and kidney were not altered.

Calcium and magnesium contents of soft tissues were not changed significantly. Both were altered in bone; the magnesium content was decreased, whereas the content of calcium was increased in proportion to the degree of magnesium deficiency produced. Thus, in those animals fed the lowest amount of magnesium, bone calcium was increased and magnesium was decreased most markedly.[20, 21, 150]

Tetany did not occur until the animals had become depleted of at least 30 per cent of their total magnesium. Despite the inadequacy of the diet, large amounts of magnesium were lost in the feces.

A spontaneous disease of beef calves raised in the vicinity of Inverness, Scotland, is identical to the experimental magnesium deficiency type. These suckling animals receive milk as the only source of magnesium. There is a gradual reduction in the mean of the serum magnesium concentration of all animals, but in a given locale not all of them develop the deficiency; those becoming deficient exhibit a continual decline in the serum concentration of magnesium. Hyperirritability and tetany appear when it falls below 1 mg. per 100 ml. The bone magnesium content of affected animals is decreased from the normal of 0.6 to 0.7 per cent to 0.3 to 0.4 per cent. Intravenous or oral administration of small amounts of magnesium only abolishes the symptoms of the disease temporarily, the feeding of 500 mg. a day prevents its appearance.[22]

Grass tetany is similar to experimental magnesium deficiency, and is characterized by hyperirritability, tetany and convulsions.[146] Hypomagnesemia always occurs in the affected cattle and the symptoms can be reversed by treatment with magnesium salts.[146, 6, 7] There is doubt, however, that this is a deficiency disease in the classic sense. It develops rapidly when cattle are turned out to spring pasture in a space of time too short for the animal to become depleted of existent stores; moreover, the magnesium content of bone is not decreased. Such a depletion of osseous magnesium is a constant finding in all other types of magnesium deficiency.

The epidemiology of this disease is unique: Cattle of all ages are affected, but only in the spring of the year. The rapidly growing grass of this season has a very high protein content, amounting to 30 per cent of the total weight. The magnesium content of the forage has been variously reported as being normal[6] or decreased.[23] However, the magnesium content of the soils is said to be normal. Only herds that are pastured in fields heavily fertilized with inorganic nitrogen, such as ammonium sulfate, are affected.[146, 7] It may be germane that the symptoms of magnesium deficiency in plants can be induced by fertilization with ammonium sulfate or ammonium nitrate and can be prevented by the addition of excess magnesium to the soil.[82] This antagonistic effect suggests that the magnesium content of grasses grown in the presence of a high soil nitrogen content is diminished.

Grass staggers may be an example of a *conditioned deficiency;*[52] the ammonium ion being the conditioning factor which interferes with the absorption of magnesium from the gut. Several facts tend to substantiate this hypothesis: the ammonium content of the rumen of diseased cows is very high. The disease can be reproduced by feeding a normal diet supplemented with ammonium carbonate in amounts sufficient to raise the ammonium content of the rumen to that encountered in the spontaneous disease. It is assumed that magnesium is poorly absorbed because of the insolubility of magnesium ammonium phosphate at alkaline pH.[75]

It has been postulated that this disease occurs because adult animals are unable to respond to an increased demand for magnesium by drawing on the bone reserves. Such animals, it is thought, cannot, therefore, meet the needs resulting from a decreased effective intake or an increased requirement attendant to the change in physical activity on being turned out to spring pasture. The normal bone magnesium content of animals with grass tetany, despite the markedly decreased amount in serum, supports this hypothesis.[23]

Experimental magnesium deficiency has been produced in dogs, rabbits, and guinea pigs.[129, 138] In most instances, the resulting diseases are similar to those described above. In the chick, however, the principal lesion is a degeneration of the Purkinje cells of the cerebellum.[19]

Pathological Alterations of Magnesium Metabolism in Man

The pathological alterations of magnesium metabolism in man were first studied in 1915 by the measurement of the intake and fecal excretion of this ion by infants with severe diarrhea.[81]

It is only very recently, however, that a clear-cut definition of magnesium deficiency in the adult human has been described, *the magnesium deficiency tetany syndrome.*[162] This syndrome is virtually identical to that of hypocalcemic tetany, from which it can be differentiated only by chemical means. Its manifestations correspond almost exactly to those seen in magnesium-deficient animals. In all patients in whom the disease has been observed, the parenteral administration of magnesium sulfate promptly and completely reversed the symptoms, signs and chemical changes of the magnesium deficiency tetany syndrome.

There was both a severe dietary inadequacy of magnesium and one or more of the following additional factors which either augmented the loss of or prevented the absorption of this ion: (1) excessive loss of magnesium from the gastrointestinal tract either by persistent vomiting or the removal of intestinal secretions by mechanical suction, (2) intestinal malabsorption and (3) the administration of large amounts of magnesium-free parenteral fluids which resulted in the formation of large urine volumes.

The patients exhibit tetany, and in addition, some have convulsions. Uniformly, the serum magnesium concentrations are depressed below 1.30 m Eq./L at the time the tetany is maximal. Treatment consists of intramuscular injection of magnesium sulfate and is followed by a prompt rise in the concentration of mag-

nesium in serum and a concomitant disappearance of tetany and convulsions. Discontinuance of magnesium sulfate therapy during the time that the conditioning factors are still operating results in a fall in the concentration of magnesium in serum accompanied by reappearance of tetany.

Conclusive proof that the syndrome is due to an alteration of magnesium metabolism is afforded by the correlation of symptoms with a chemical change in serum, and by the concomitant restoration of both to the normal state by treatment with magnesium. In all instances, there is a direct correlation between the existence of tetany, the decreased concentration of magnesium in serum, and the disappearance of tetany when the serum magnesium is restored to normal.

In view of the close similarity between the manifestations of magnesium and calcium deficiencies, it is only reasonable that questions should arise concerning the interrelationships of the resultant syndromes. In our studies,[162] calcium concentrations in the serum of patients suffering from magnesium deficiency tetany have been within the normal range. Similar observations have been made by others.[45, 46, 54, 121] Some observers, however,[70] have questioned the lack of involvement of calcium in magnesium deficiency tetany. The finding of low serum magnesium and normal calcium concentrations in patients who did *not* exhibit tetany, constituted the basis of their critique, although according to the authors, two of the three patients did have a positive Chvostek's sign.

In this regard, it should be emphasized that final decisions as to whether the magnesium tetany deficiency syndrome exists are based on the presence of the following constellation: (1) tetany and its attendant manifestations, (2) a low serum magnesium concentration, (3) normal serum calcium concentration, (4) normal blood pH, and (5) prompt relief of tetany with the restoration to normal of the serum magnesium concentration.

Consequently, a patient who fails to exhibit any one of the first four features is not a suitable subject for the verification of the hypothesis that one may be dealing with this disease, nor, for that matter, can the efficacy of treatment with magnesium be tested in a meaningful manner under such circumstances. Clearly an hypothesis can only be accepted or rejected when examined in an appropriate experimental setting. Thus, the absence of tetany in the presence of low serum magnesium concentration cannot serve to reject the existence of the syndrome. In our experience, the total serum magnesium concentration at which tetany may be observed varies from 1.3 to 0.4 m Eq./L, a considerable spread.

Similar and analogous observations have been made in lambs.[111] The reasons for this are not clear. It should be pointed out, however, that 35% of the serum magnesium is bound to protein. The metabolism of calcium may be pertinent here since it is of course, well known in regard to clinical effects, that the ionized fraction of the serum calcium is much more significant than the total serum calcium concentration. Hence, failure to observe clinical consequences in the presence of a decreased total serum magnesium concentration may reflect no more than a shift in the equilibrium between the total and ionizable fractions of magnesium in serum. Such measurements of ionizable magnesium in relation to

magnesium deficiency tetany are not as yet on record. However, the important question, i.e., the existence of magnesium deficiency tetany in the absence of any disturbance of calcium metabolism can be examined. We have recently had the opportunity to perform some crucial experiments in this regard.

A patient suffering from severe malnutrition due to resection of almost the entire small bowel was studied over a period of eight weeks. The pertinent data are summarized in Table I. He suffered from (1) tetany and attendant clinical manifestations, (2) the serum magnesium concentration was decreased to 0.4 m Eq./L, (3) the serum calcium concentration was normal, (4) blood pH was normal, and (5) tetany disappeared on the administration of magnesium.

TABLE I

Magnesium Deficiency Tetany Due to Massive Resection of the Small Bowel

Day	Serum Ca^{++} m Eq./L	Serum Mg^{++} m Eq./L	Serum HCO_3 m Eq./L	Blood pH	Tetany	Therapy
1	4.5	0.4	23.9	7.29	Present	0.08 gm Ca^{++} I.V.
3	4.2	0.4			Present	0.16 gm Ca^{++} I.V.
5	4.1		22.9	7.30	Present	600,000 units Vitamin D I.M.
8	4.5	0.4	21.0	7.26	Present	
9	4.9	0.3			Present	0.4 gm Mg^{++} I.V.
10	5.0	1.75			Absent	0.4 gm Mg^{++} I.V.
11	5.0	2.18			Absent	0.4 gm Mg^{++} I.V.
19	4.7	1.4			Absent	

In regard to this patient, it should be emphasized that at the beginning of the period of study the calcium concentration of his serum was slightly decreased. Subsequently it returned to normal coincident with the administration of vitamin D; the serum magnesium concentration, however, did not increase. Despite the restoration of the serum calcium to normal, tetany persisted until the serum magnesium concentration was returned to normal by the parenteral administration of magnesium.

These data indicate the existence of a specific syndrome of magnesium deficiency tetany in which the administration of magnesium is a specific, crucial and potentially life saving measure.

Clinical Manifestations of the Magnesium Deficiency Tetany Syndrome

Clinically the human magnesium deficiency syndrome is indistinguishable from hypocalcemic tetany. It is manifested by the presence of either Chvostek's, Trousseau's or Von Bornsdorff's sign when tetany is latent, or by frank carpopedal spasm when tetany is active. As in hypocalcemic tetany, the neuromuscular irritability is aggravated by mechanical, auditory or visual stimulation. The similarity to hypocalcemic tetany is further increased by the presence of a lowered threshold response to galvanic stimulation.[166]

The manifestations of human magnesium deficiency are virtually identical to those occurring spontaneously or which may be induced experimentally in numerous animal species. Tetany is the primary sign of lack of magnesium and, like the human syndrome, it is indistinguishable from hypocalcemic tetany except by the measurement of the serum concentration of the two ions. The magnesium deficiency tetany syndrome, therefore, is one of the rare illnesses of man which mimics almost exactly a corresponding disorder of animals.

Conditioning Factors

Dietary restriction alone does not produce magnesium deficiency tetany nor does prolonged debilitation. Malnutrition has been a factor in all of our patients and a reduced dietary intake of magnesium occurred in most. Whenever the syndrome has been observed, it was brought about or intensified by some other factor which either prevented the absorption or increased the excretion of magnesium. This description fits the definition of *conditioned deficiencies* in which the normal intake of nutrients does not meet the needs of an organism owing to the presence of unusual circumstances or factors.[52] Failure to absorb a metabolite, inability to synthesize it into a biologically active intermediate and excessive excretion are the simplest examples of conditioning factors.

In our series, the conditioned deficiency appeared against a background of severe debilitating disease, prolonged acute infections, severe malnutrition on the basis of alcoholism complicated by alcoholic gastritis and excessive emesis, intestinal obstruction followed by postoperative drainage of intestinal contents and intestinal malabsorption subsequent to radiation therapy or surgical excision of the small bowel. Magnesium deficiency tetany, therefore, is most likely to develop in a setting of decreased intake and excessive loss of the element, in the presence of severe debilitating illness, as might be seen in patients subjected to surgery or treated for long periods of time with magnesium-free fluids.

A review of the literature reveals that this syndrome has been observed before, although it has not been delineated sharply in its true context.[109, 69, 102, 119] Low serum magnesium concentrations have been reported to occur in postoperative patients maintained on prolonged nasogastric suction and magnesium-free fluids given parenterally; symptoms of magnesium deficiency tetany have been reported in some but not in others. A detailed study of the response of such patients to the parenteral administration of magnesium salts has not been reported, although case reports of individual patients of this type who have been treated indicate that the therapy was prompt and effective.

Several instances of hyperaldosteronism with concurrent tetany have been reported. The serum calcium concentrations were normal but the serum magnesium concentrations were markedly depressed.[107, 120] Similarly, tetany following the removal of parathyroid adenomas has been associated with the presence of low concentrations of magnesium in serum.[13, 4]

Ever since the original description of magnesium deficiency in rats by McCollum,[90] objections to the use of the term "tetany" to describe the symptoms have been voiced.[70] Therefore, it is well to clarify the semantic implications of this designation. It does not suggest a definitive cause; the word denotes a syndrome of diverse origins. Nevertheless, it has sometimes — and erroneously — been regarded as synonymous with, and diagnostic of, alterations in the state of the serum calcium. Actually, in addition to deficiencies of calcium or magnesium, tetany may be the result of exposure to a number of toxic substances, being guanidine, strychnine, lead, tetanus toxin, and chlorophenothane, (DDT).[61]

Underlying Mechanisms

The biochemical and physiological mechanisms by which a deficiency of either calcium or magnesium produces tetany are unknown. One may consider the interactions of these ions with the energy-generating processes of mitochondria [134, 135, 99, 164] and their effects on enzymatic reactions[58-162] and on nerve and muscle membrane potential[26, 142, 143, 131, 115, 50, 62, 58] as indications of potentially important loci of their action.

On purely phenomenological grounds, their physiological actions on isolated components of the neuromusclar system present a model system in which to explore the possible mechanism underlying the syndrome.

Nerve conduction, transmission at the myoneural junction and muscle contraction are affected crucially, although differently, by magnesium and calcium. A decreased concentration of both magnesium and calcium lowers the threshold to stimulation of motor nerves. Increased irritability results because of a charge effect on the membrane. Conversely, the excitatory threshold is increased by an increase in the concentration of either ion.[62, 58] In muscle, on the other hand, the effects of calcium and magnesium are antagonistic; low concentrations of magnesium intensify contractions and low concentrations of calcium inhibit them; these responses result from interactions with a number of interrelated enzyme systems.

At the myoneural junction, both charge and enzymatic effects operate jointly, making this the most complex of the three potential sites of action of magnesium and calcium on the neuromuscular apparatus. The critical parameters are the quantity of acetylcholine liberated, the activity of acetylcholine-esterase and the state of excitability of the presynaptic nerve and muscle membrane.[26, 142, 50, 39]

Integrating these complex relationships it may be said that an increase in transmission at the motor end plate is the overall result of the decrease in the concentration of magnesium or calcium. Low concentrations of magnesium lower the excitatory thresholds of the presynaptic nerve and of the muscle membrane

and increase the liberation of acetylcholine. Low concentrations of calcium also lower the excitatory thresholds of the presynaptic nerve and muscle membrane, but in contrast to magnesium, decrease the liberation of acetylcholine. The overall effect of low concentrations of calcium is to increase the transmission of the nerve impulse. Decreased concentrations of magnesium increase irritability through increased nerve conduction, increased transmission of the impulse at the myoneural junction and increased contractility, i.e., at all these three loci of the neuromuscular apparatus here singled out for inspection. This is brought about through a summation of enzymatic and charge effects.

Magnesium Metabolism in Other Conditions

Since magnesium deficiency is manifested by aberrations of the neuromuscular system, a host of human diseases have at one time been attributed to a deficiency of this element. Although some of these have been found to be accompanied by a decrease in the concentration of magnesium in serum, in no instance, so far, has a causal relationship to magnesium deficiency been demonstrated except in the magnesium deficiency tetany syndrome.

Delirium tremens has received considerable attention in this regard in recent years. The discovery of a reduced serum concentration of magnesium in patients with chronic alcoholism and delirium tremens[154, 55] coupled with a similarity of the symptoms of delirium tremens and magnesium deficiency in animals, led to the hypothesis that this disease is due to magnesium deficiency.[55, 57] Although the serum concentration of magnesium is reduced in many patients with delirium tremens, this finding has not been consistent. Moreover, although the response of some of these patients to the parenteral administration of magnesium appeared to be beneficial, controlled studies of magnesium treatment of delirium tremens were not conclusive in demonstrating a one to one therapeutic effect.

The observations made on one of our patients with magnesium deficiency tetany are enlightening in regard to this question.[162] This chronic alcoholic was admitted to the hospital because of persistent vomiting secondary to a severe alcoholic gastritis following a six-week bout of alcoholism. At the time of his admission, severe tetany was present. Before magnesium therapy could be instituted he experienced several grand mal seizures. However, within 12 hours of the start of parenteral magnesium therapy, all the symptoms and signs of tetany had disappeared; concomitantly the serum magnesium concentration rose from extremely low levels to within the normal range. At this time, the patient was lucid and essentially asymptomatic. Despite the administration of magnesium which raised the serum concentration to normal and abolished the tetany, it failed to prevent the appearance of delirium tremens. Delirium tremens occurred two days later when the concentrations of all serum electrolytes, including magnesium, were normal. It appears, therefore, that delirium tremens may develop and progress despite continuous treatment with magnesium salts and, in fact, while the concentration of magnesium in serum is normal. Thus, these findings virtually eliminate the possibility that magnesium deficiency is the direct cause of delirium tremens. These observations clearly delineate magnesium deficiency tetany from

delirium tremens. Magnesium deficiency tetany may occur in patients in whom alcoholism is not even a factor. It may also develop in malnourished patients who may be chronic alcoholics, but in whom delirium tremens does not occur. It may appear in patients who develop delirium tremens later. Finally, these two conditions may actually co-exist. The remarkable improvement observed in some patients with delirium tremens subsequent to therapy with magnesium salts may thus be ascribed to concurrent but unrecognized magnesium deficiency tetany. The elucidation of this complex situation should allow these two diseases to be identified and treated even when both are present.

Decreased serum concentrations of magnesium have also been reported to occur in many other human diseases. These include idiopathic epilepsy,[74] eclampsia,[79] chronic nephritis,[79, 110] patients with congestive heart failure treated with ammonium chloride and mercurial diuretics,[110] and acute pancreatitis,[47] diabetic acidosis,[8, 29] and cirrhosis of the liver.[152, 56]

Summary

The clinical manifestations of human magnesium deficiency tetany are indistinguishable from those of hypocalcemic tetany. The two conditions must be differentiated by chemical analysis. Magnesium deficiency tetany in man closely simulates the accompaniments of magnesium deficiency in animals.

Sustained losses of gastrointestinal secretions, prolonged parenteral fluid therapy or severe infection acted as conditioning factors to produce the syndrome in previously malnourished persons. The clinical manifestations of the disease consist of tetany with carpopedal spasm, or positive Chvostek's, Trousseau's or Von Bonsdorf's signs, convulsions, athetoid movements of the extremities and marked reaction to mechanical and auditory stimulation. In all instances, the concentration of magnesium in serum is markedly depressed whereas that of calcium is normal.

In all patients with magnesium deficiency tetany, parenteral administration of magnesium sulfate promptly and completely reverses the symptoms, signs and chemical changes of the disease.

Original work reported in this paper has been supported by grants-in-aid from the National Institutes of Health, The Nutrition Foundation and the Lasdon Foundation.

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